

For which patients shall the drug work, and how?

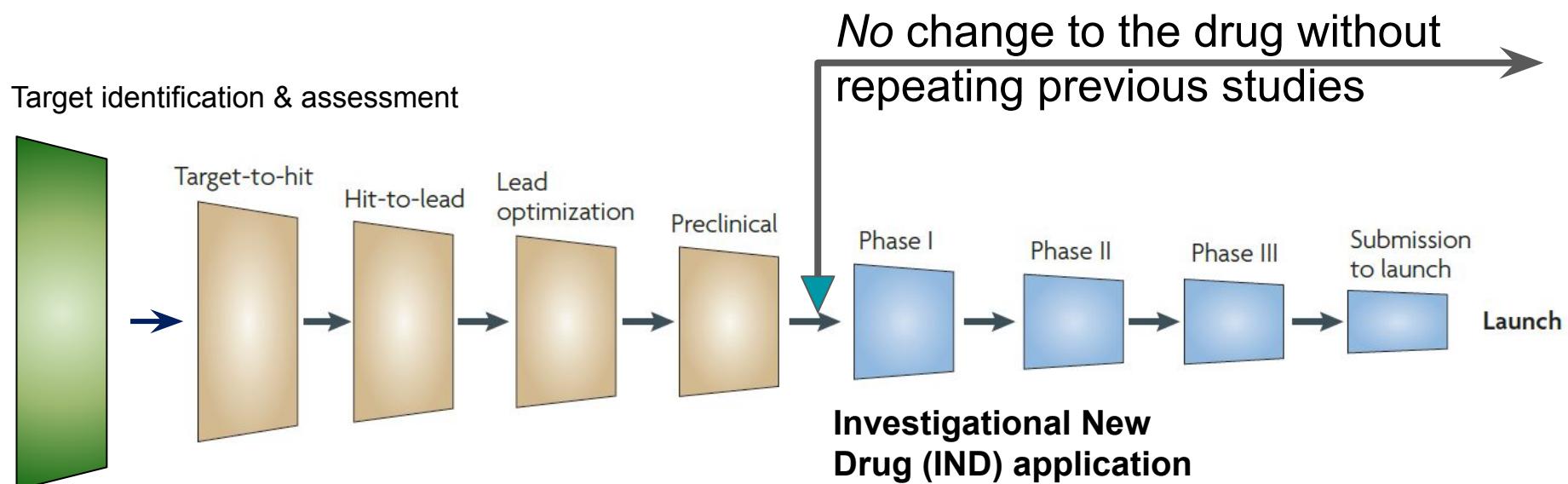
Mathematical and Computational Biology in Drug Discovery (MCBDD)
Module V

Dr. Jitao David Zhang
May-June 2021

Outline of Module V

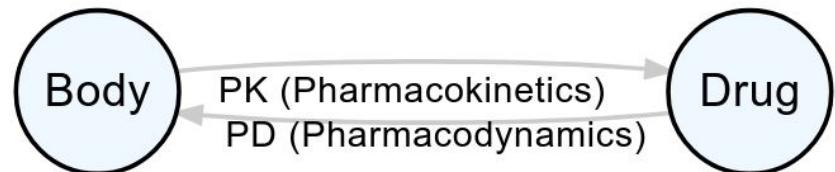
- Lecture 11
 - Biomarker for dose prediction
 - Biomarker for patient-stratification and biology understanding: Merck/Genentech
 - Challenges and caveats
- Lecture 12
 - Integrating statistical and mechanistic modelling: Griffiths *et al.*
 - Mechanistic modelling of biological systems: from Boolean network to Agent-based modelling
 - Causal inference

From drug discovery to drug development

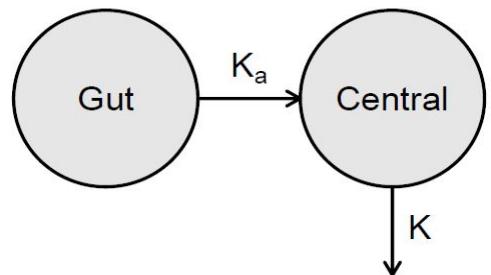


A refresher of PK/PD Modelling

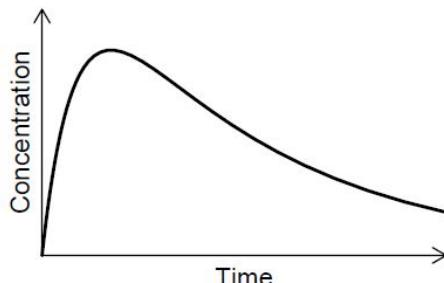
(A)



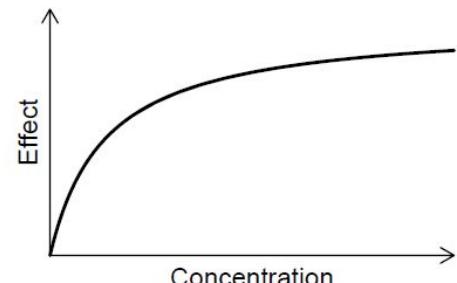
(B)



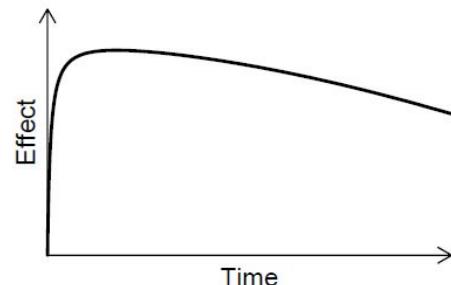
(C)



(a) PK model



(b) PD model



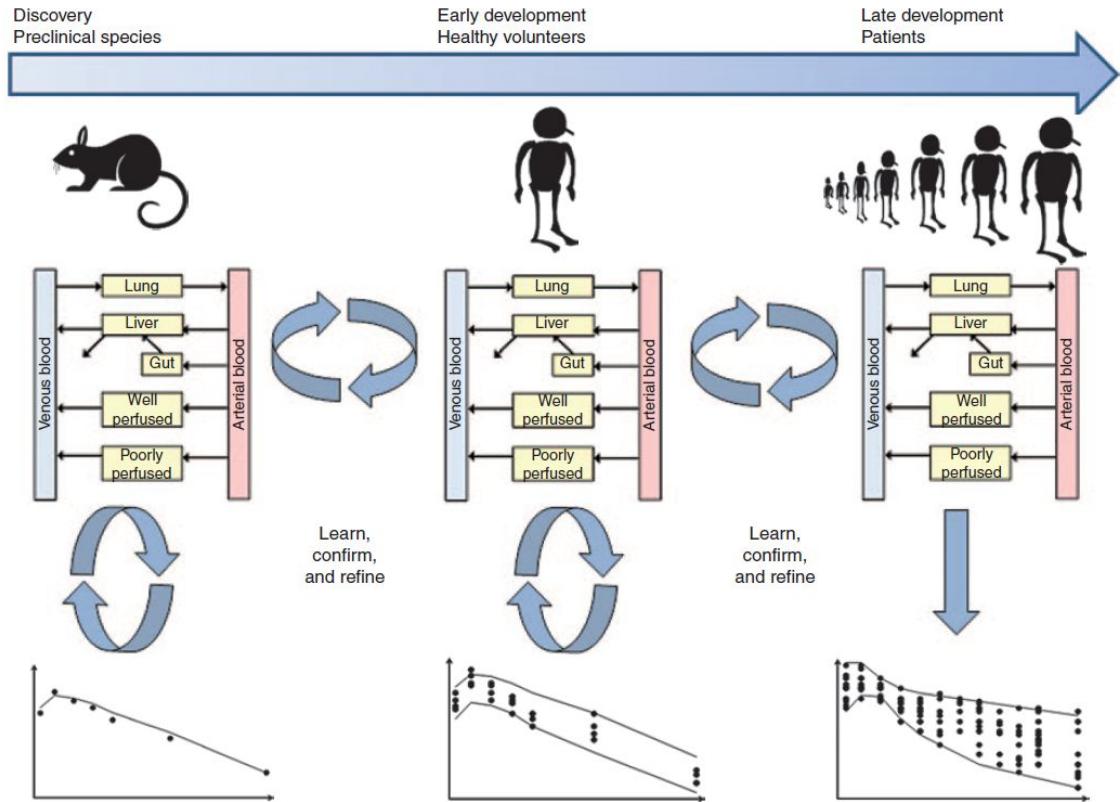
(c) Combined PK/PD model

$$\frac{dA_{gut}}{dt} = -K_a \cdot A_{gut}$$

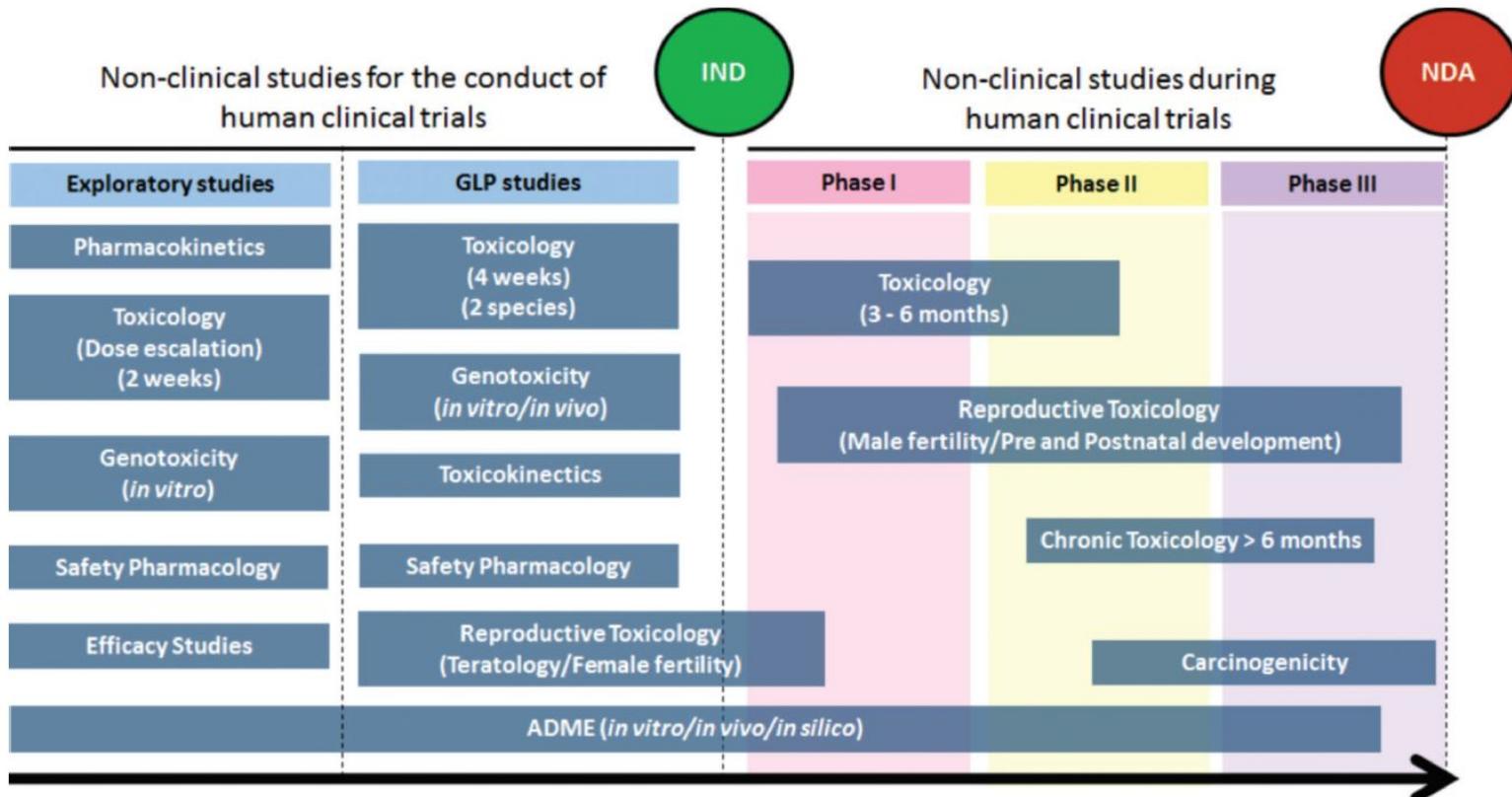
$$\frac{dA}{dt} = \underbrace{F \cdot K_a \cdot A_{gut}}_{\text{from gut}} - \underbrace{K \cdot A}_{\text{elimination}}$$

$$A_{oral}(t) = \frac{K_a F A_0}{K_a - K} (\exp(-K \cdot t) - \exp(-K_a \cdot t))$$

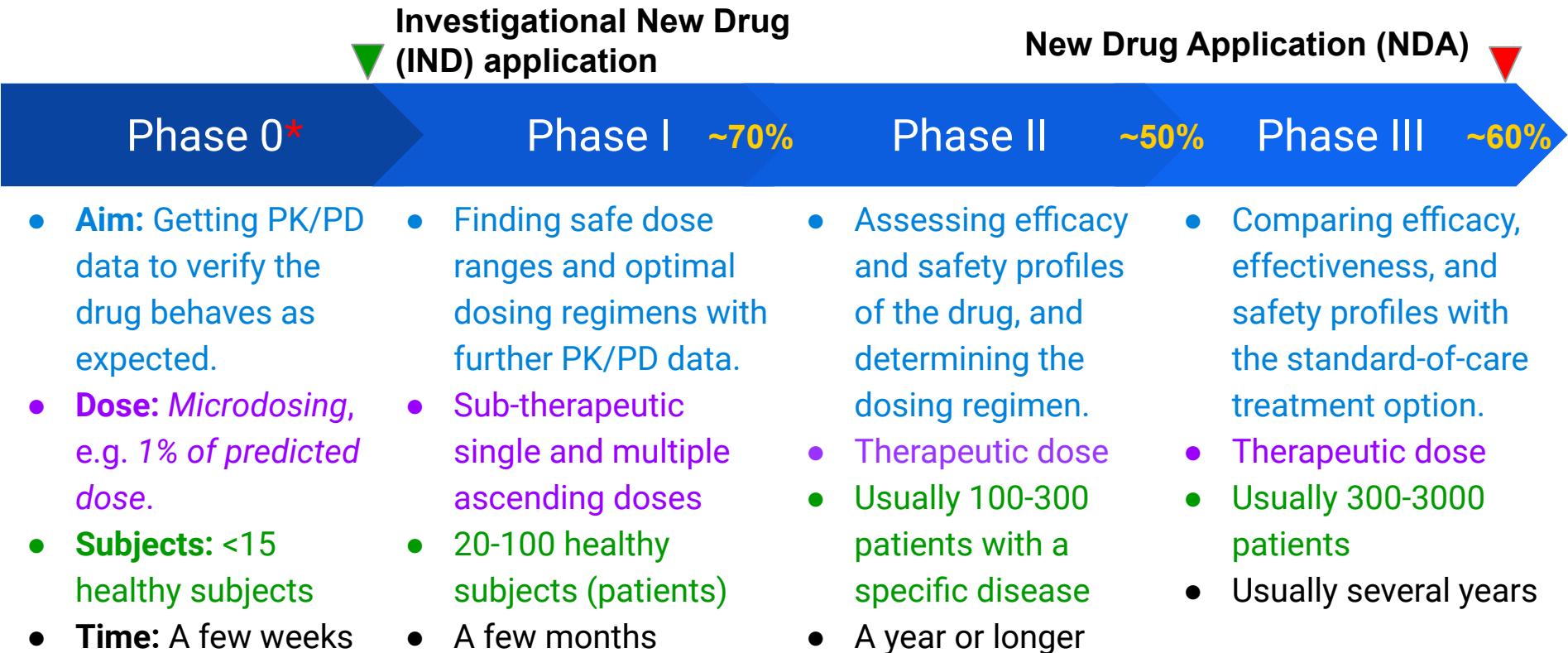
Physiologically-based pharmacokinetic modelling (PBPK) is a natural extension of PK modelling



Non-clinical studies continue during drug development



Phases of clinical trials



Empirical, stratified, and individualized medicine



Empirical medicine

- Vaccines
- Non-steroid anti-inflammatory drugs (NSAIDs)

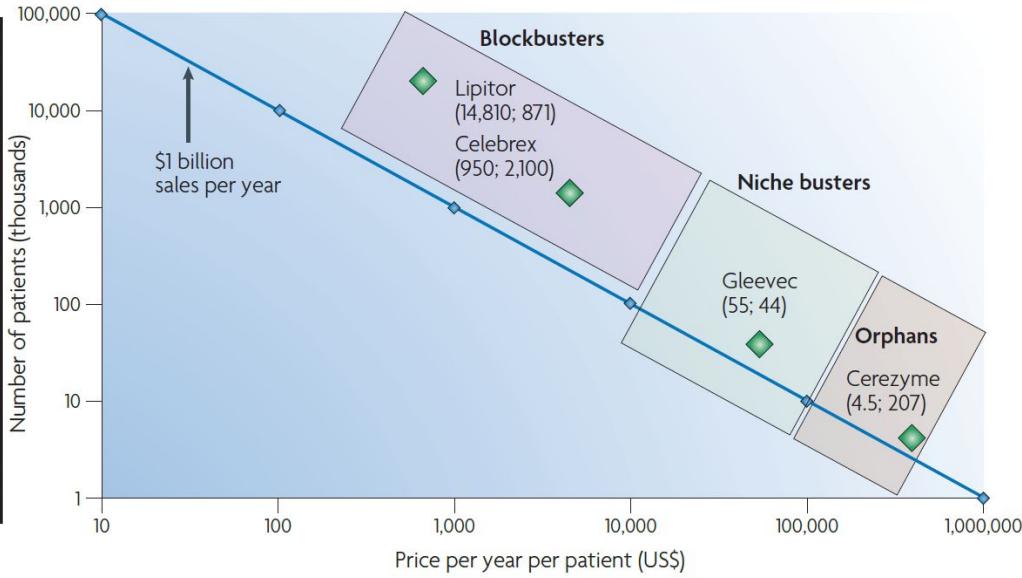
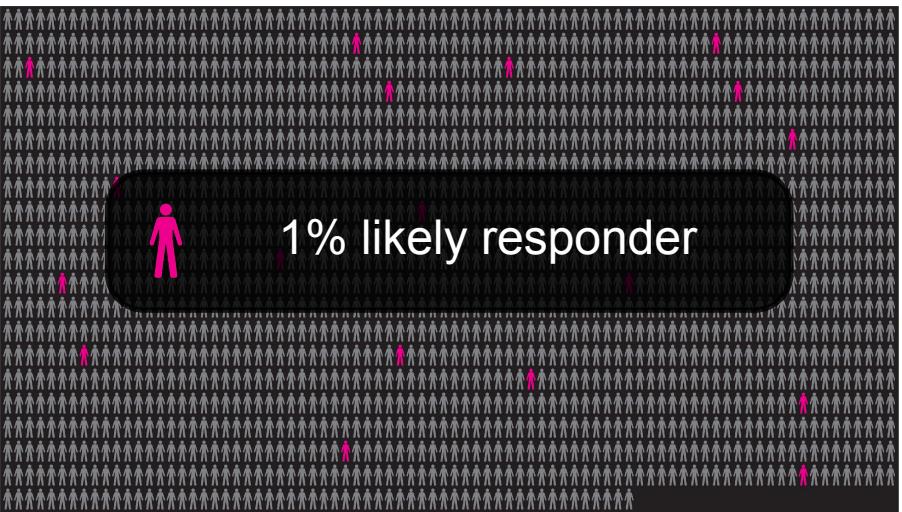
Stratified Medicine

- Vemurafenib (Zelboraf)
- Trastuzumab (Herceptin)

Individualized medicine

- CAR-T therapy

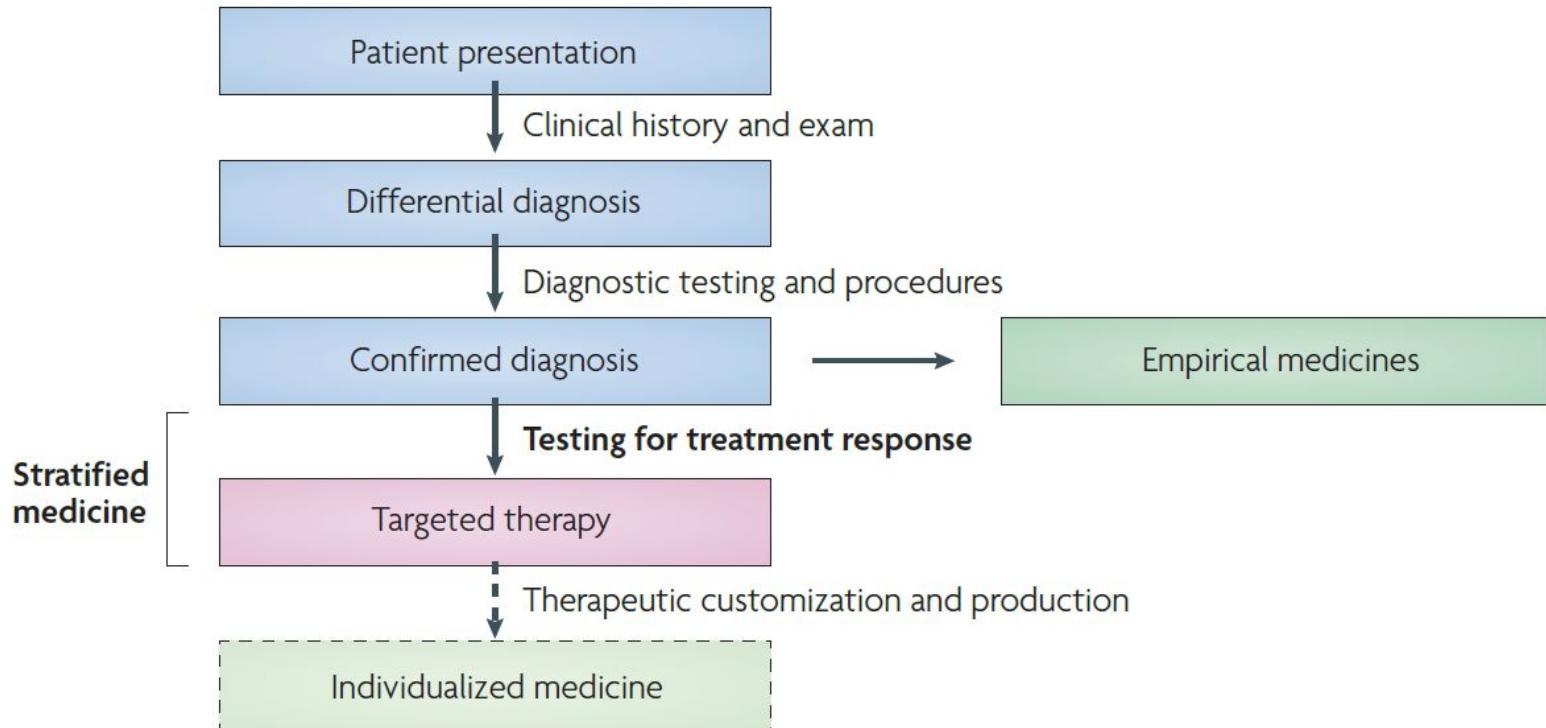
Why stratified medicines are becoming popular?



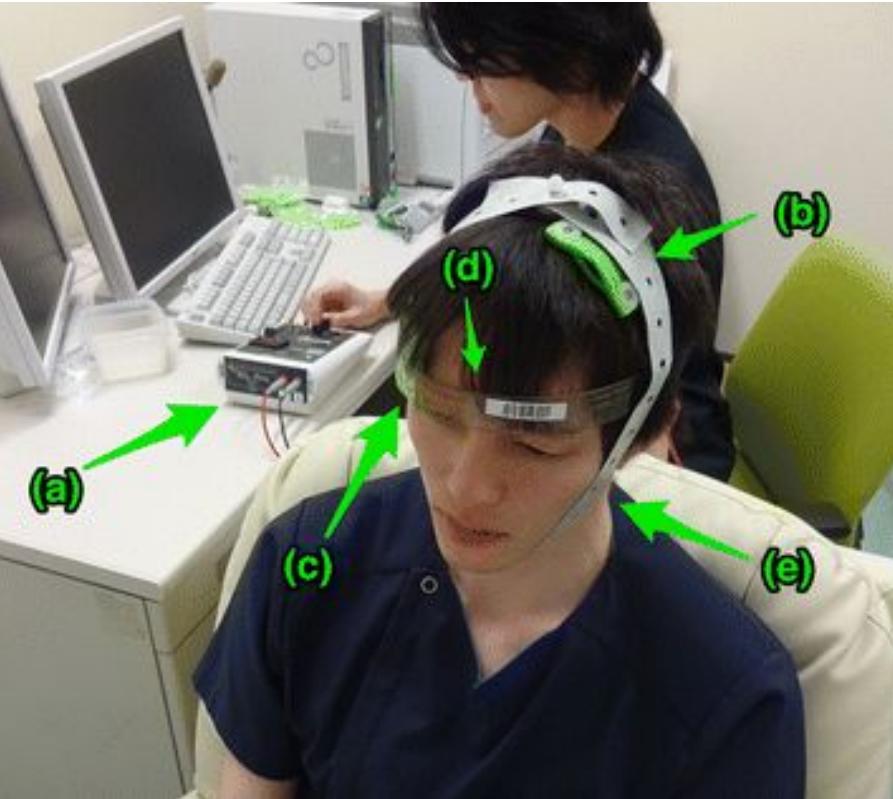
Medical reasons

Commercial reasons

Empirical, stratified, and individualized medicine in the clinical context



Transcranial Direct Current Stimulation (tDCS)



Transcranial Direct Current Stimulation (tDCS)

LIFTID tDCS Gerät zur Verbesserung von Fokus, Aufmerksamkeit, Gedächtnis und Produktivität

Marke: LIFTID

Preis: **169,00 €**

Preisangaben inkl. USt. Abhängig von der Lieferadresse kann die USt. an der Kasse variieren. [Weitere Informationen](#).

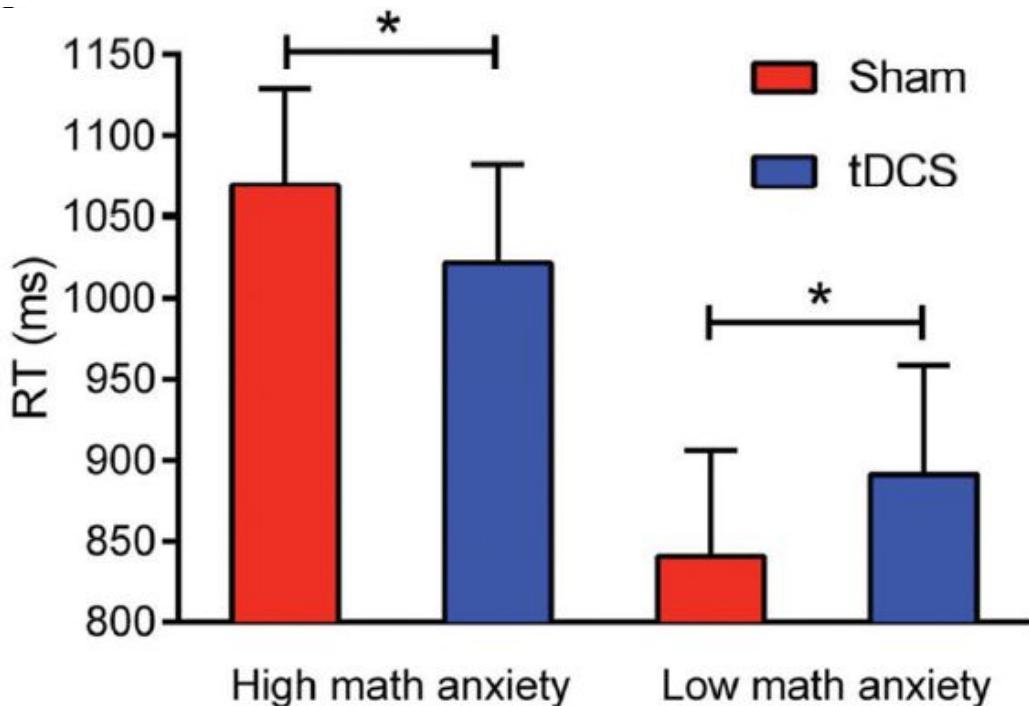
Ausgaben im Blick behalten und **8€ Aktionsgutschein** sichern: Jetzt Amazon-Konto aufladen [Mehr erfahren](#)



- Verbessern Sie Ihre Leistung: Entwickelt für Gamer, Studenten, vielbeschäftigte Profis, Musiker und Sportler. Jeder kann LIFTID verwenden, um seine Leistung zu erhöhen, es dauert nur 20 Minuten, um LIFTID während Ihrer Lieblingsaufgabe zu verwenden.
- tDCS leicht gemacht: leicht (nur 70 Gramm), keine Kabel und einfach zu bedienen (Plug 'n Play). Einfach die Pads anfeuchten, aufsetzen und losdrücken. Gerät läuft automatisch für 20 Minuten bei 1,2 mA.
- Reisesicher: Wiederaufladbarer, langlebiger Lithium-Ionen-Akku. Vergessen Sie die Suche nach einem 9V Akku, der LIFTID Gerät Akku ist langlebig und schnell zu laden. Liftid ist eine Freisprecheinrichtung und benötigt keine Basiseinheit. Absolut tragbar. Verwenden Sie es beim Sitzen, Stehen, Gehen oder Dehnen.

Not tested in randomized clinical trials
(<https://clinicaltrials.gov>)

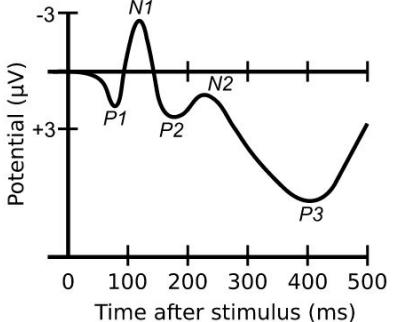
Cognitive Enhancement or Cognitive Cost? It depends!



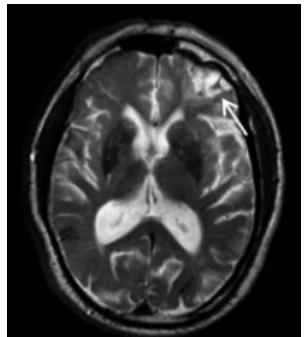
Biomarkers

A objectively measured and evaluated characteristic as an indicator of (1) normal biological process, (2) pathogenic processes, or (3) pharmacological responses to a therapeutic intervention.

Electro-physiological



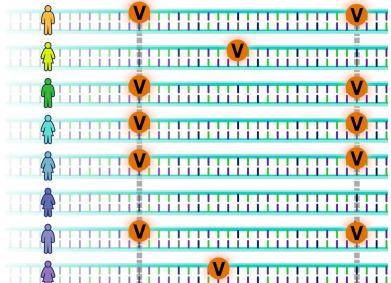
Imaging



Functional

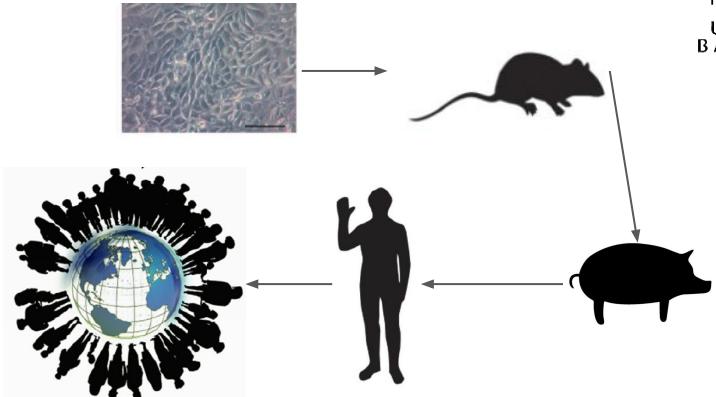


Molecular



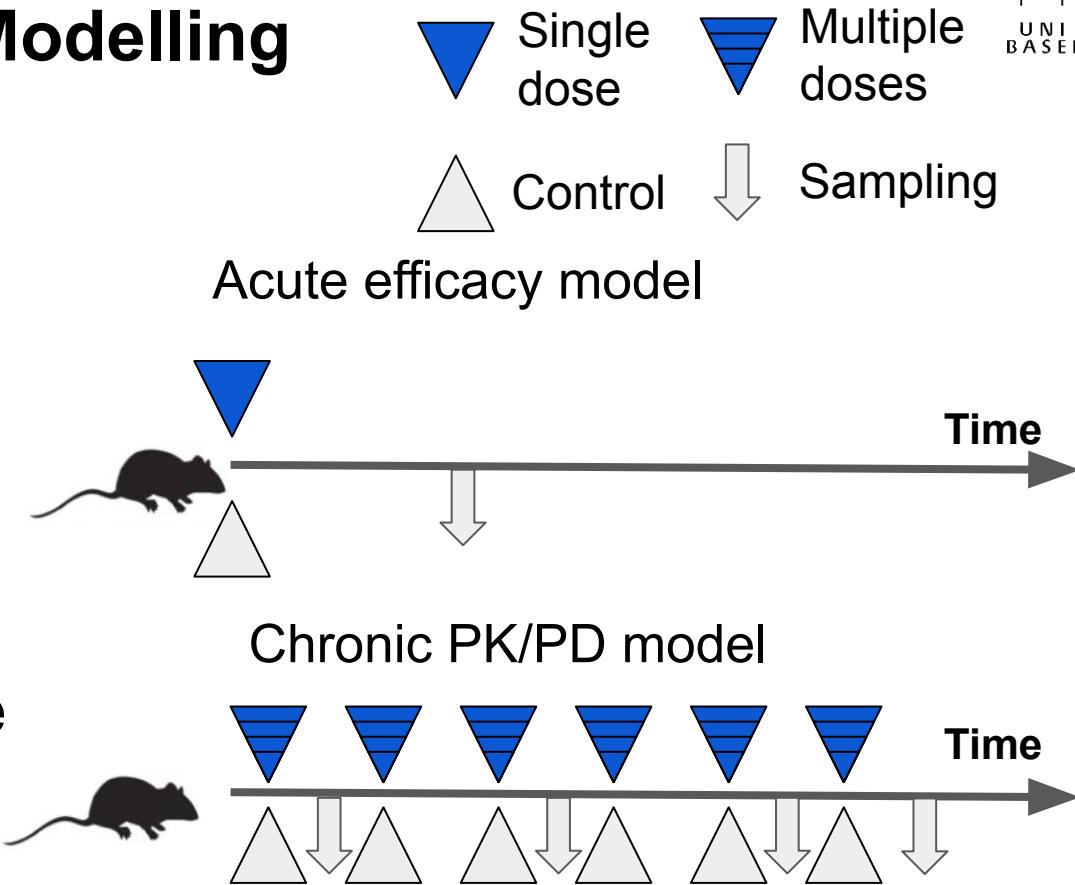
Applications of biomarkers

1. Compound optimization and differentiation from competitors in preclinical study
2. Human-dose prediction in translational PK/PD modelling
3. Patient stratification in clinical studies



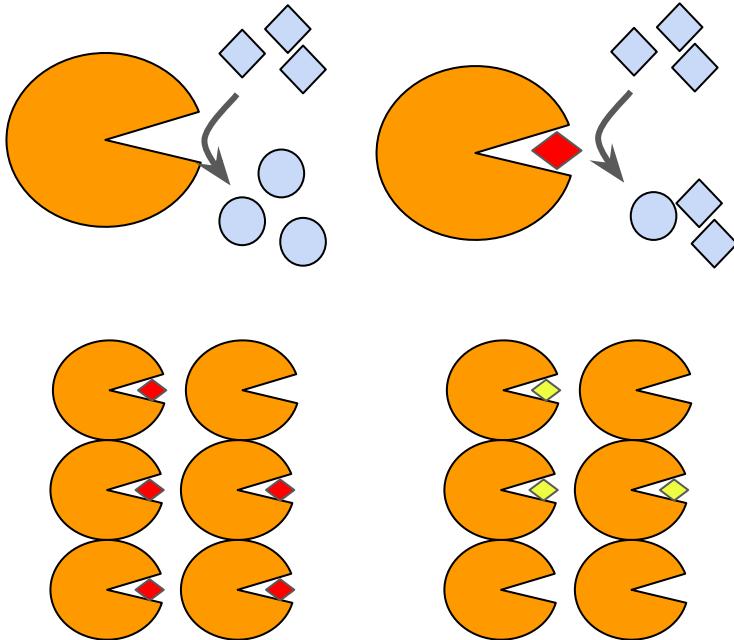
Translational PK/PD Modelling

Samples from blood and the target organ can be analysed for pharmacokinetics, pharmacodynamics, and dose-exposure-response relationships.



Target Occupancy as Biomarkers

Target occupancy, percentage of the protein target occupied by drugs, affects **target engagement**, which describes the process a drug interacts with its intended protein target in a living system to induce downstream effects (Mechanism of Action).

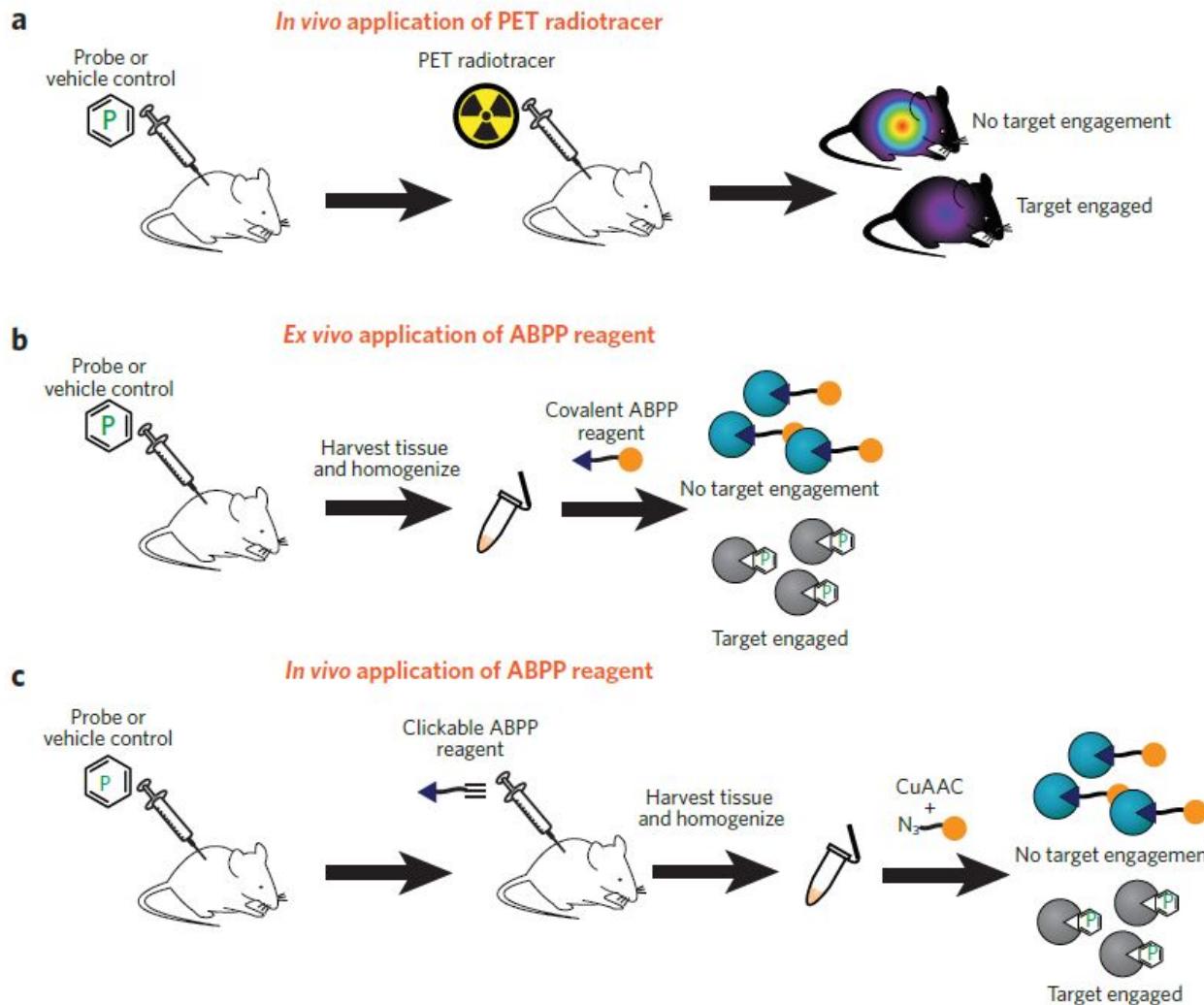


Target occupancy of 83% and 50%, respectively

Target occupancy and engagement profiling in vivo

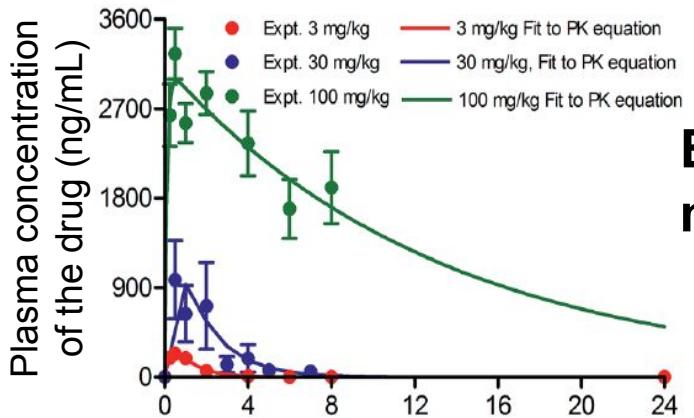
ABPP: Activity-based protein profiling; PET: positron-emission tomography.

Both ABPP reagent and radiotracer binds to the same protein target.

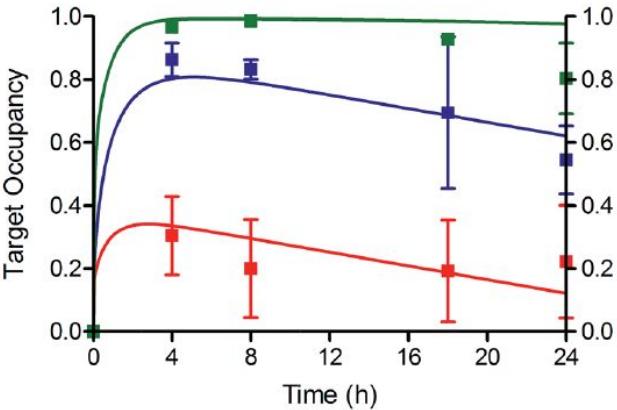


Target occupancy as a biomarker links pharmacokinetics and pharmacodynamics

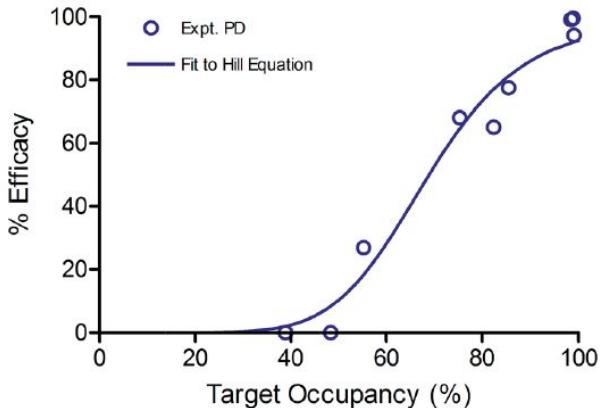
PK modelling



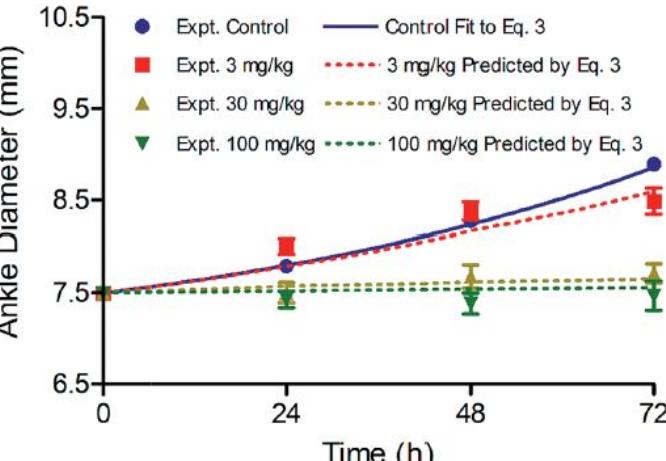
Biomarker modelling



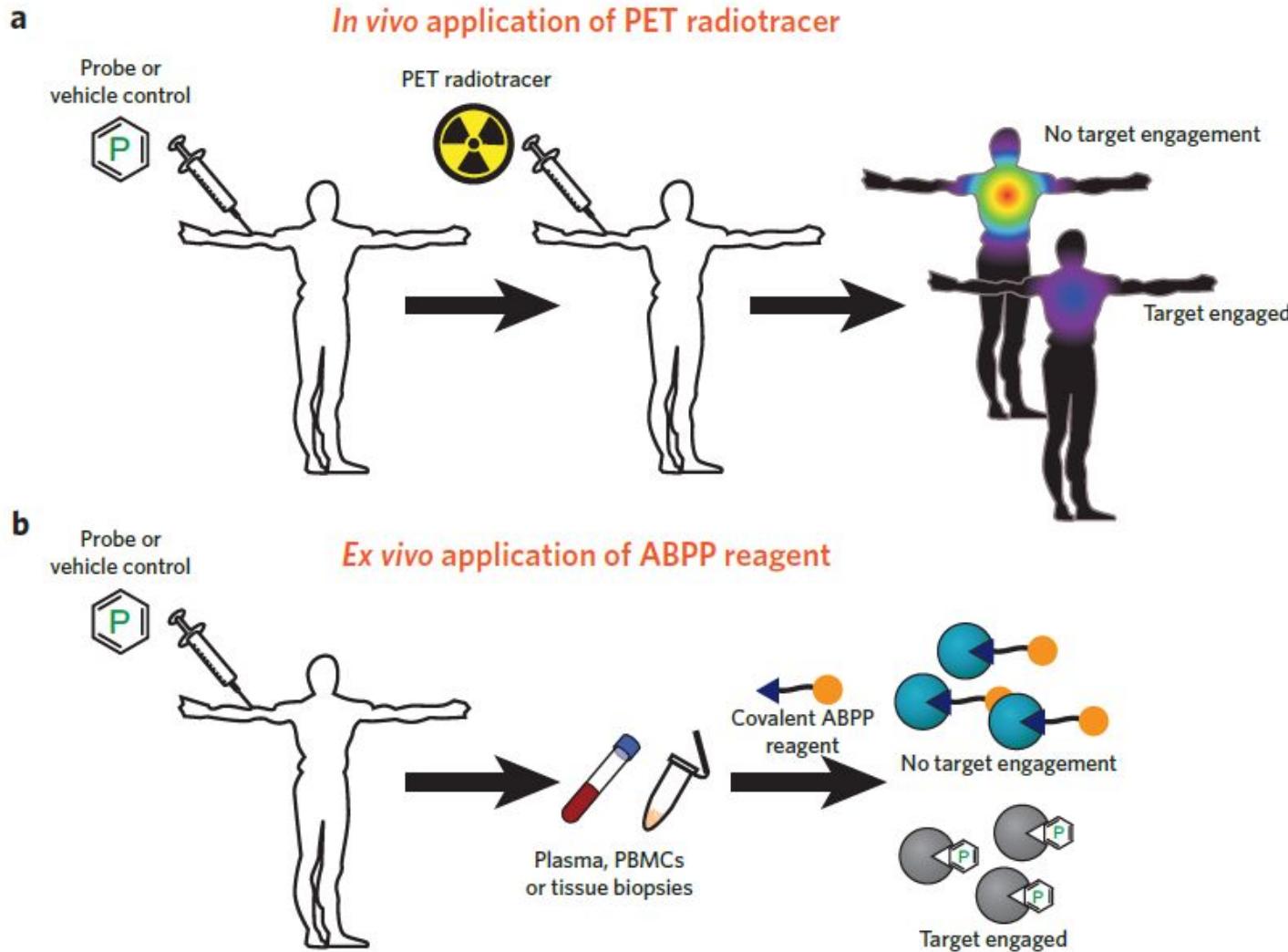
PD modelling



PK/PD modelling



Target occupancy and engagement profiling in human

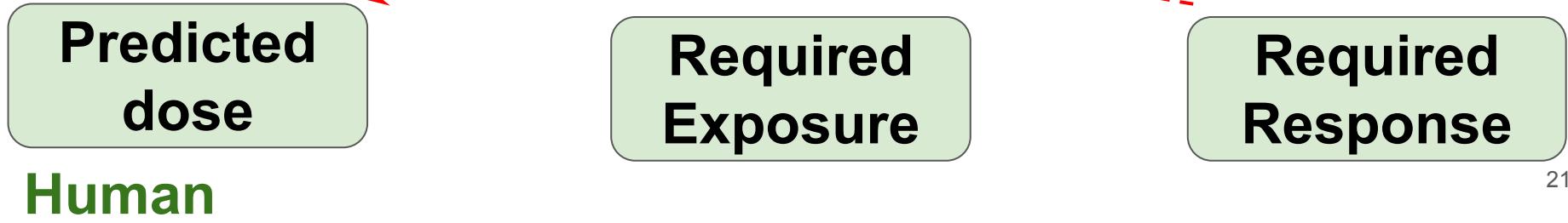


A mental model of biomarker for human-dose prediction

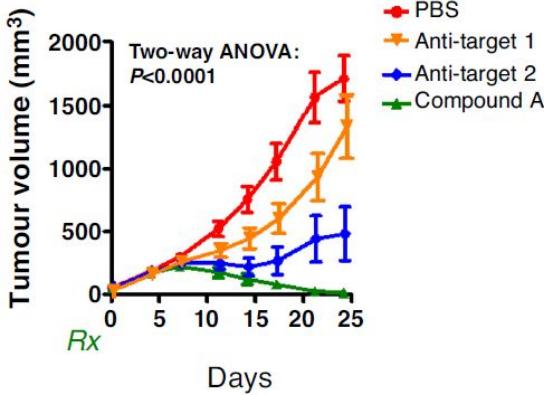
Animal model



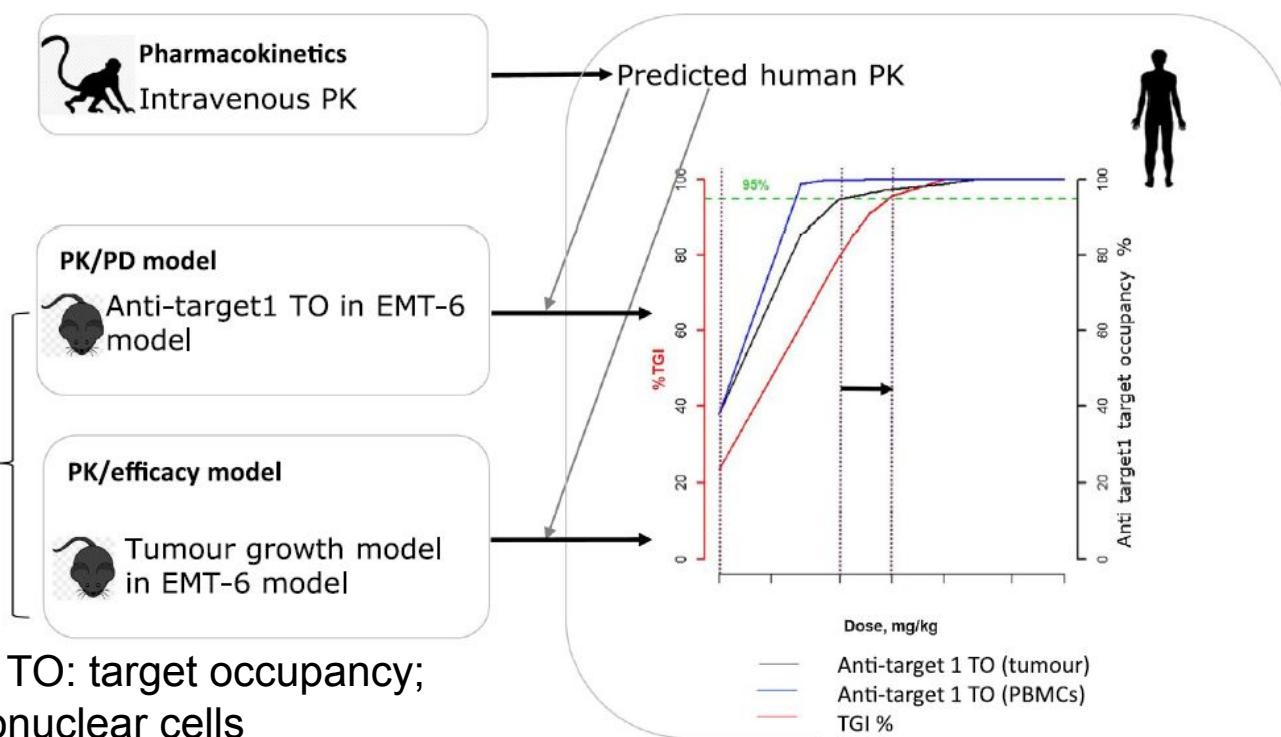
Translational biomarker
(e.g. Target occupancy in PBMC and in tumour)



A real-word example with a bispecific antibody



Anti-target 1 TO required for efficacy in tumour and PBMCs
 Efficacious concentration



TGI: tumour growth inhibition; TO: target occupancy;
 PBMC, peripheral blood mononuclear cells

Exposure-response in animal model and translatable biomarkers are essential for dose prediction

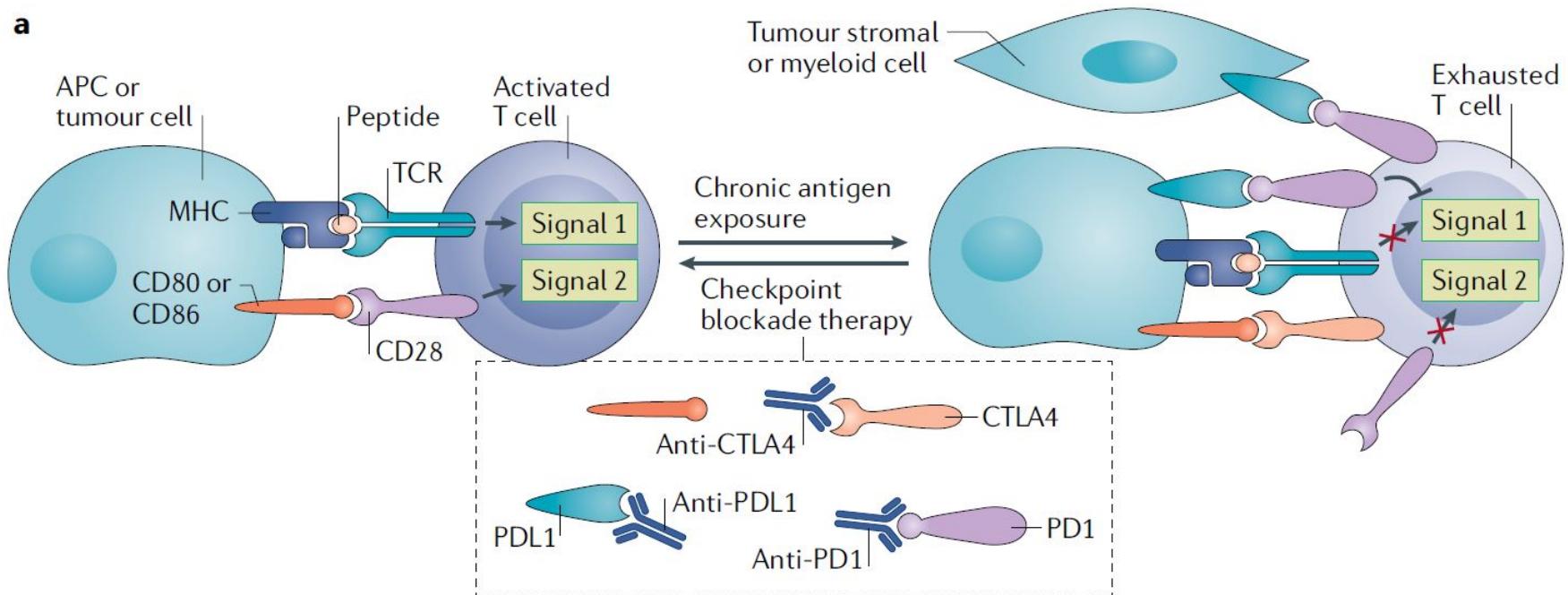
TABLE 2

Correlation of responses to dose-related questions (Q) of TmX Guide to dose prediction successes or observation of efficacy in the clinic

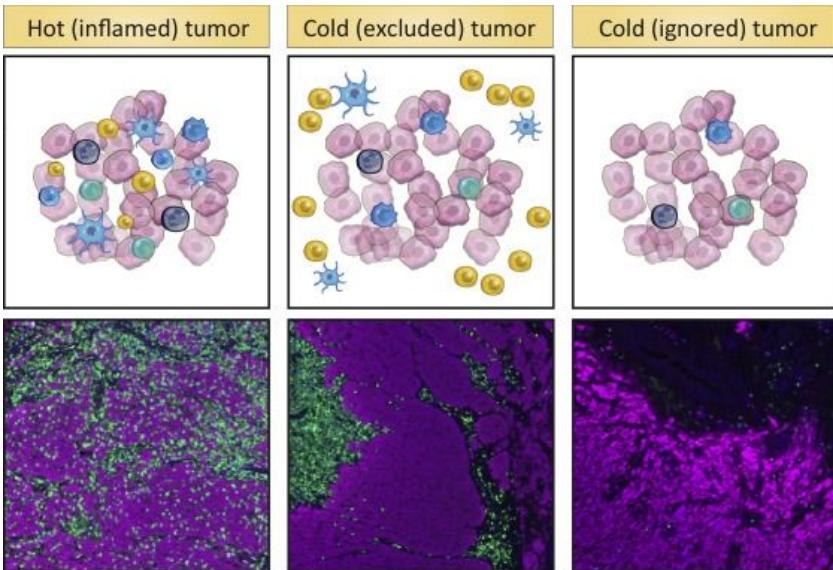
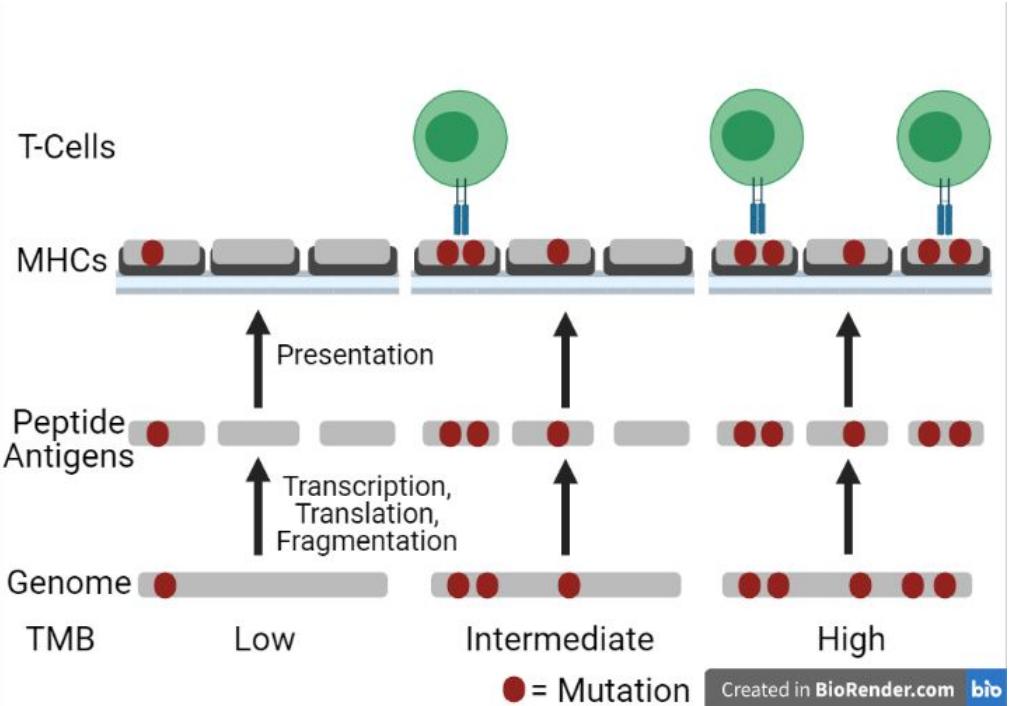
Category	Q1: desired exposure-response in appropriate animal model?	Q2: Translatable biomarkers?	Number of drugs for which model-based active dose prediction is within twofold or clinical efficacy is observed within predicted dose range out of total number in category
1	Yes	Yes	5/6
2 ^a	No	No	1/6
3	No	Yes	2/2
4 ^b	Yes	No	0/1

Molecular basis of cancer immunotherapy

a



Tumour mutation burden and immune phenotype may affect the effect of immunotherapy

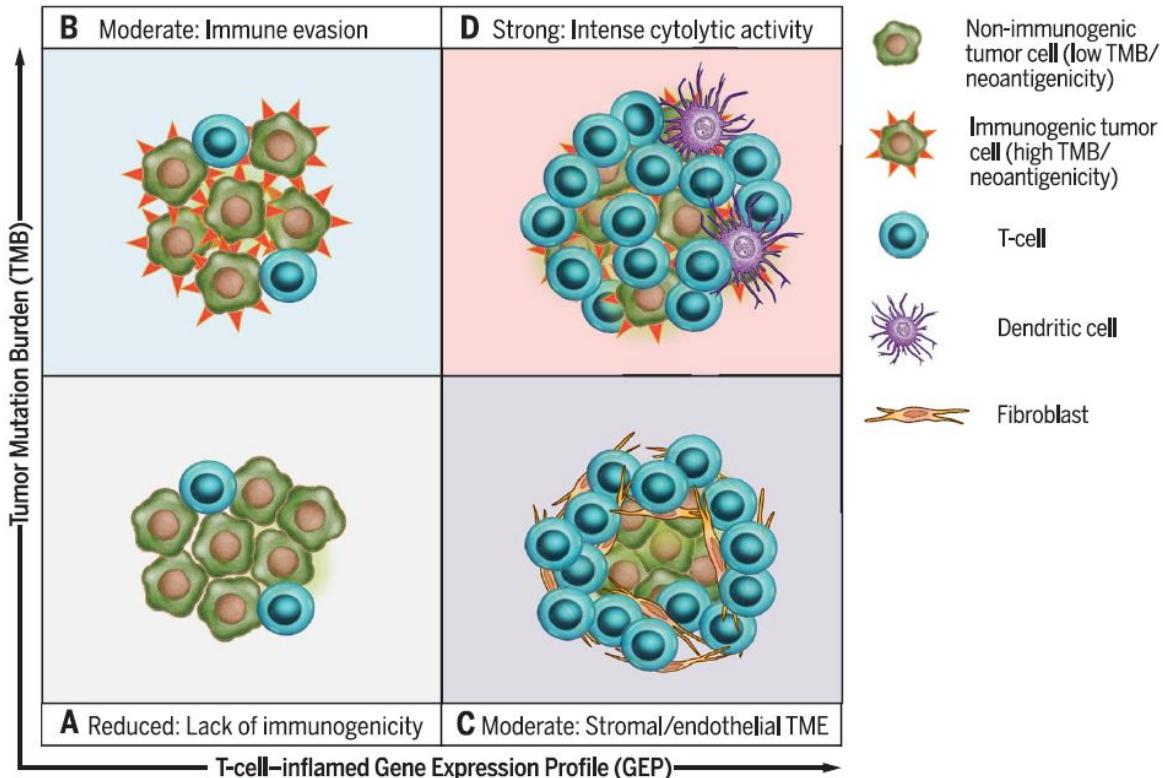


Trends in Cancer

MHC: Major Histocompatibility Complex; TMB: Tumour Mutation Burden.

Cristescu et al. established TMB and T-cell-inflamed Gene Expression Profile (GEP) as biomarkers

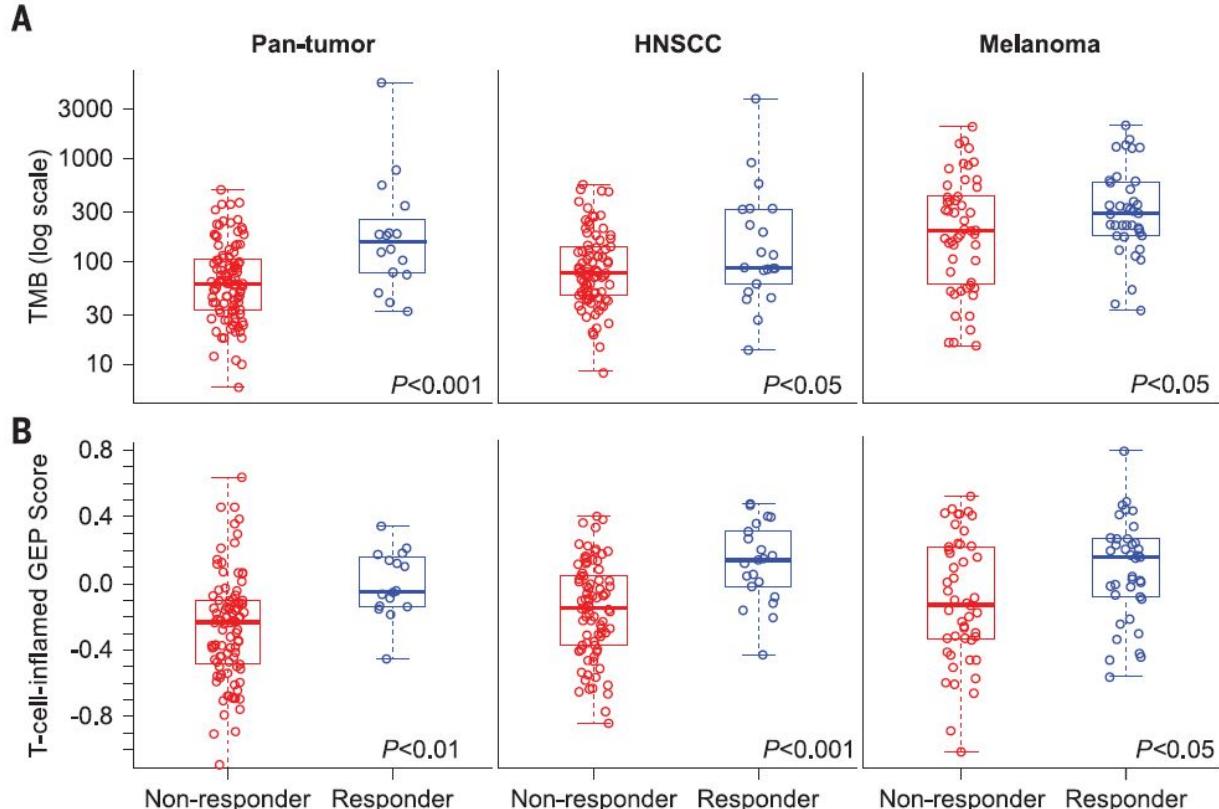
Patients with high tumor mutation burden **AND** a T-cell-inflamed gene expression profile (TME) are more likely to respond to cancer immunotherapy.



Univariate analysis establishes correlation between TMB/GEP and responsiveness

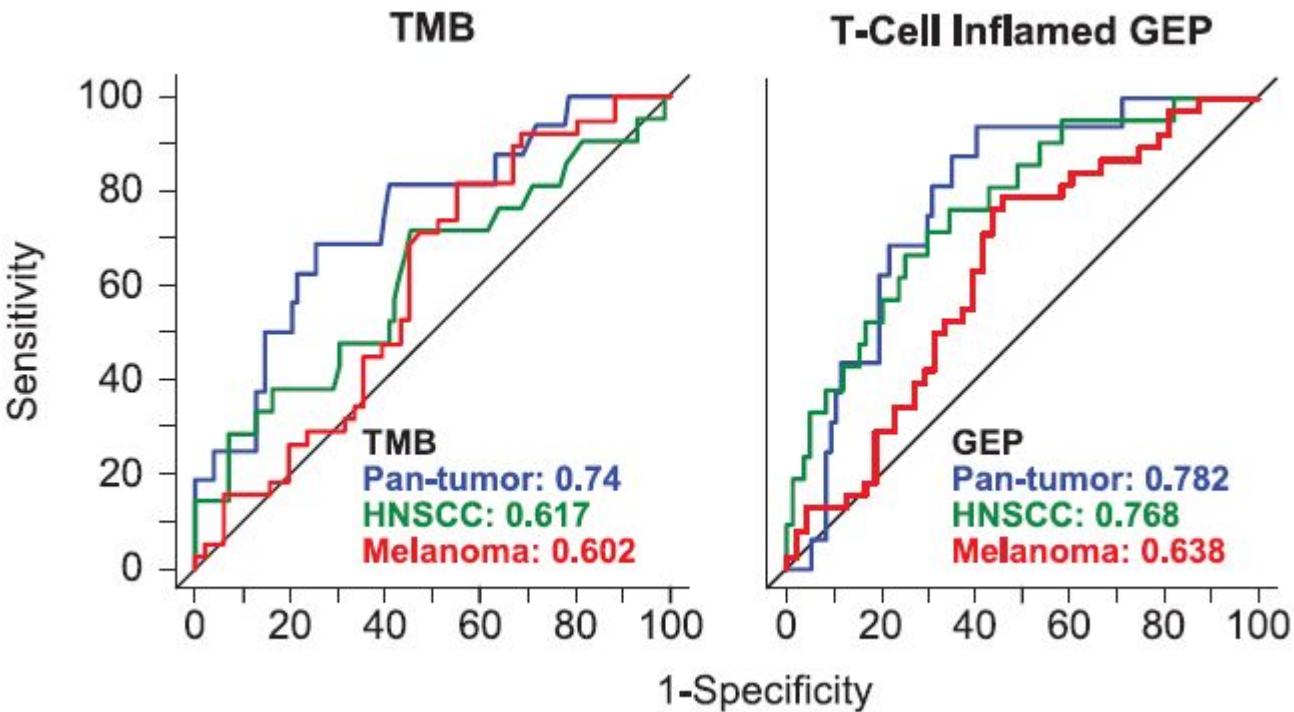
GEP: weighted sum of normalized expression of 18 genes related with immune response (CCL5, CD27, CD274 (PD-L1), CD276 (B7-H3), CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2 (PDL2), PSMB10, STAT1, and TIGIT).

HNSCC: head and neck cancer



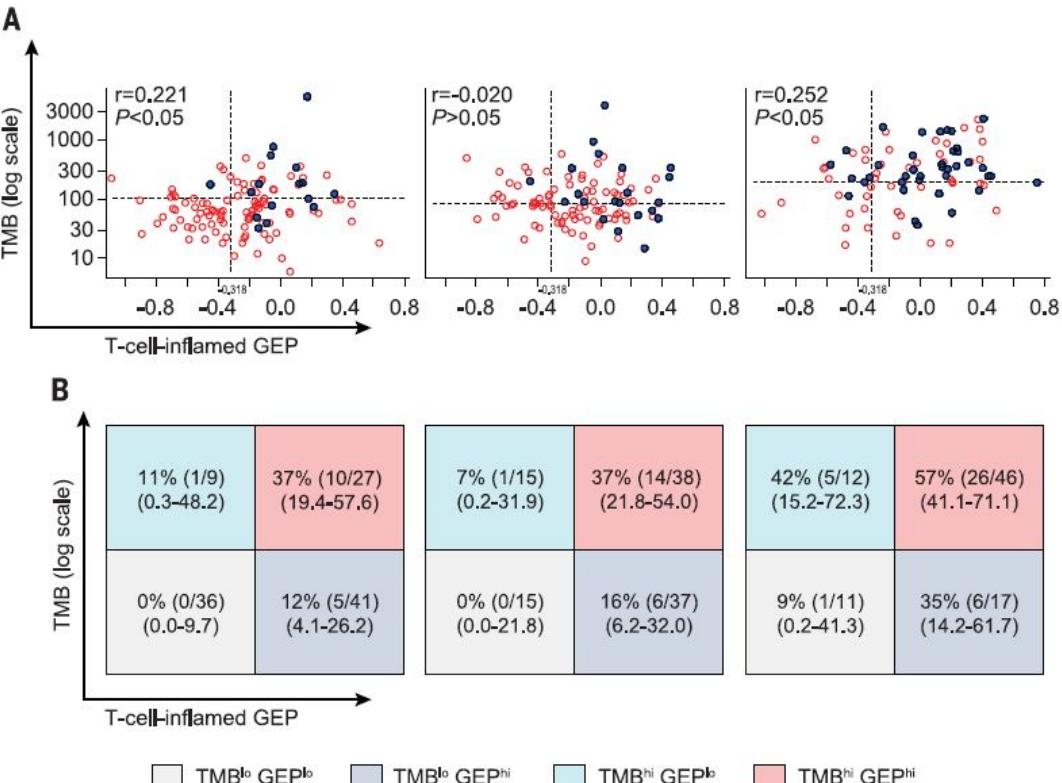
Both TMB and GEP can partially predict responsiveness

Receiver
 Operating
 Characteristic
 (ROC) curves of
 using either TMB
 or GEP for binary
 classification.
 Metrics: Area
 Under ROC
 (AUROC)

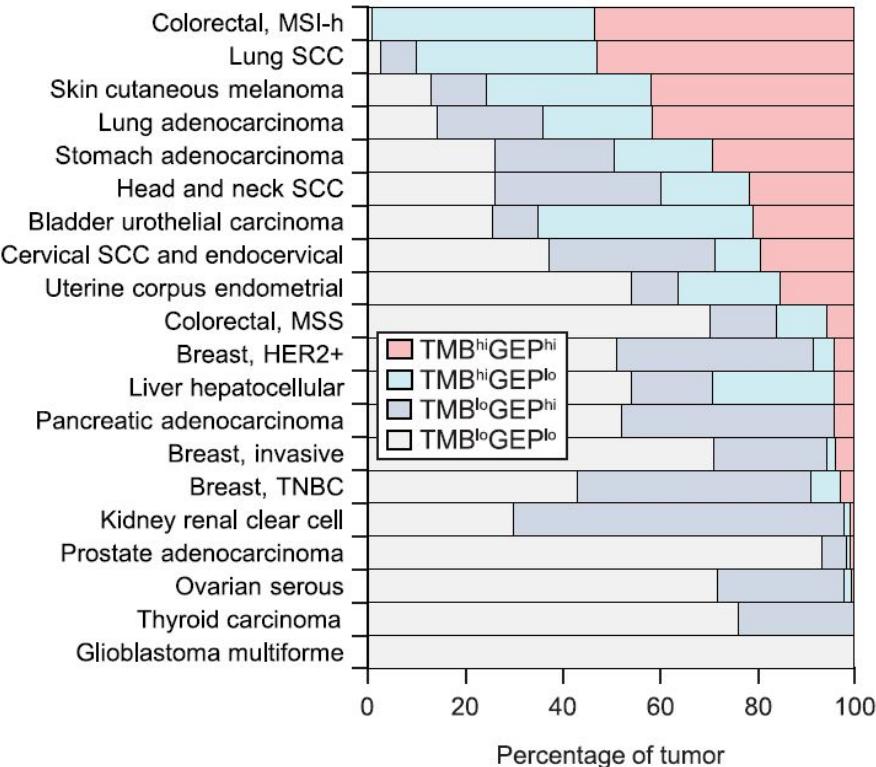
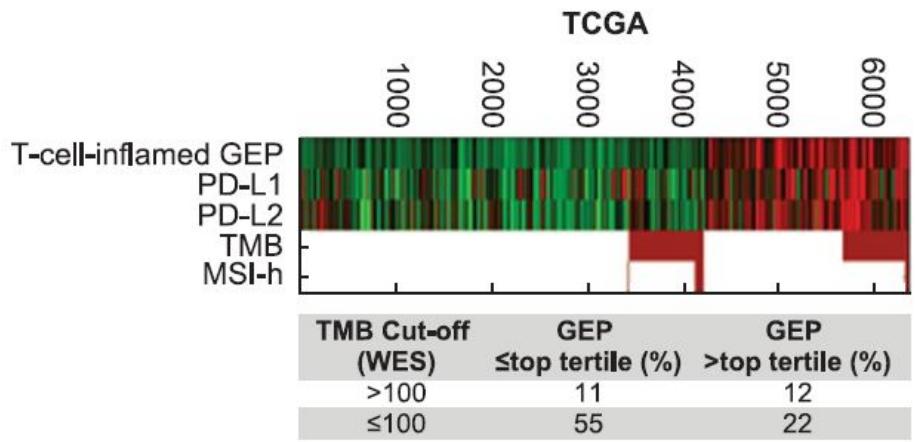


High TMB and high GEP are associated with higher responsiveness to anti-PD1 antibody treatment

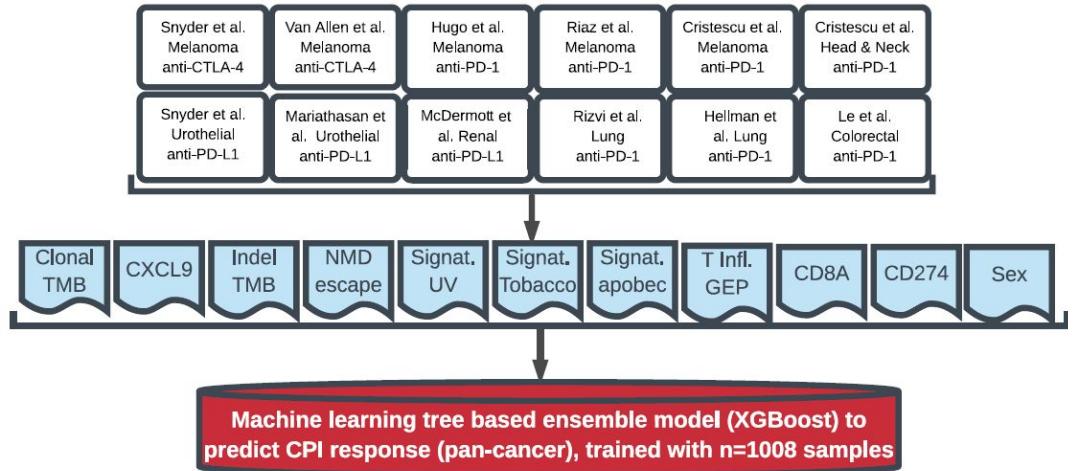
- From left to right: three patient cohorts (pan-cancer; head-and-neck cancer; melanoma)
- Open red circles: non responders; Black dots: responders.



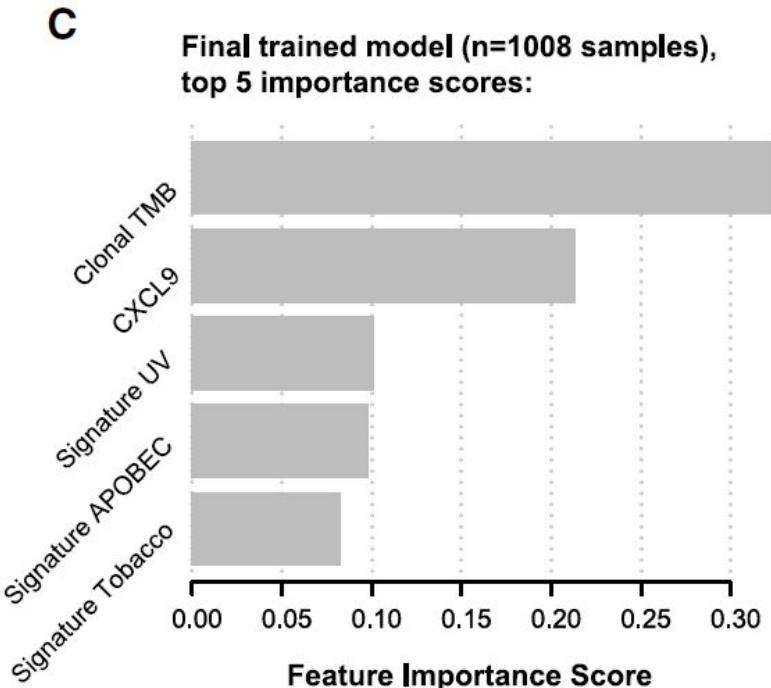
Data mining in public cancer database TCGA suggests potential indications



Meta-analysis (Litchfield et al. 2021) confirms TMB and T-cell infiltration as predictors of responsiveness

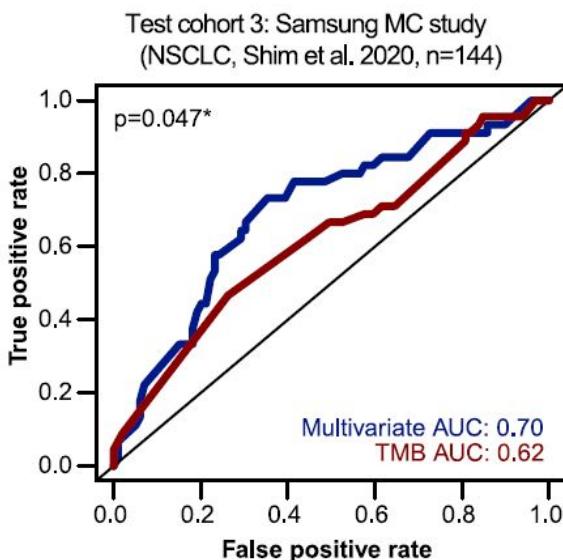
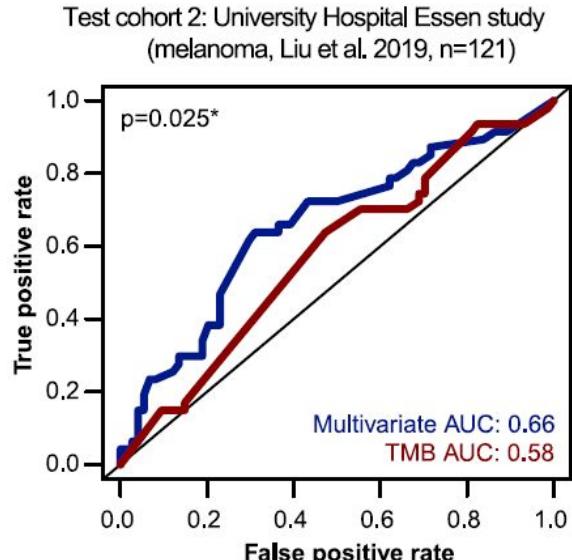
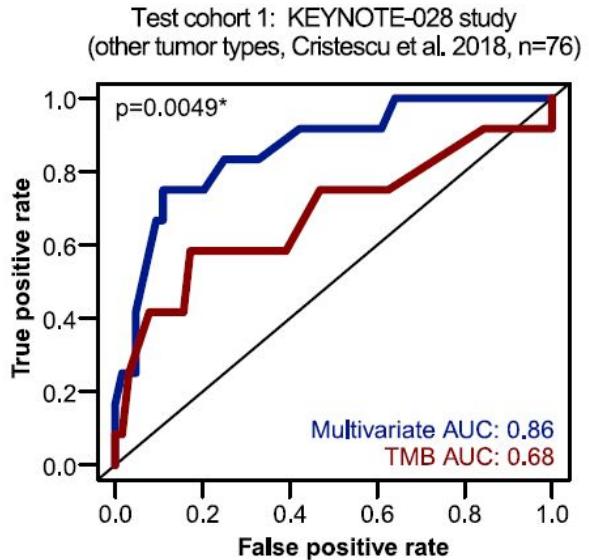


CXCL9 is a chemokine that enhances recruitment of cytotoxic CD8⁺ T cells into the tumor.



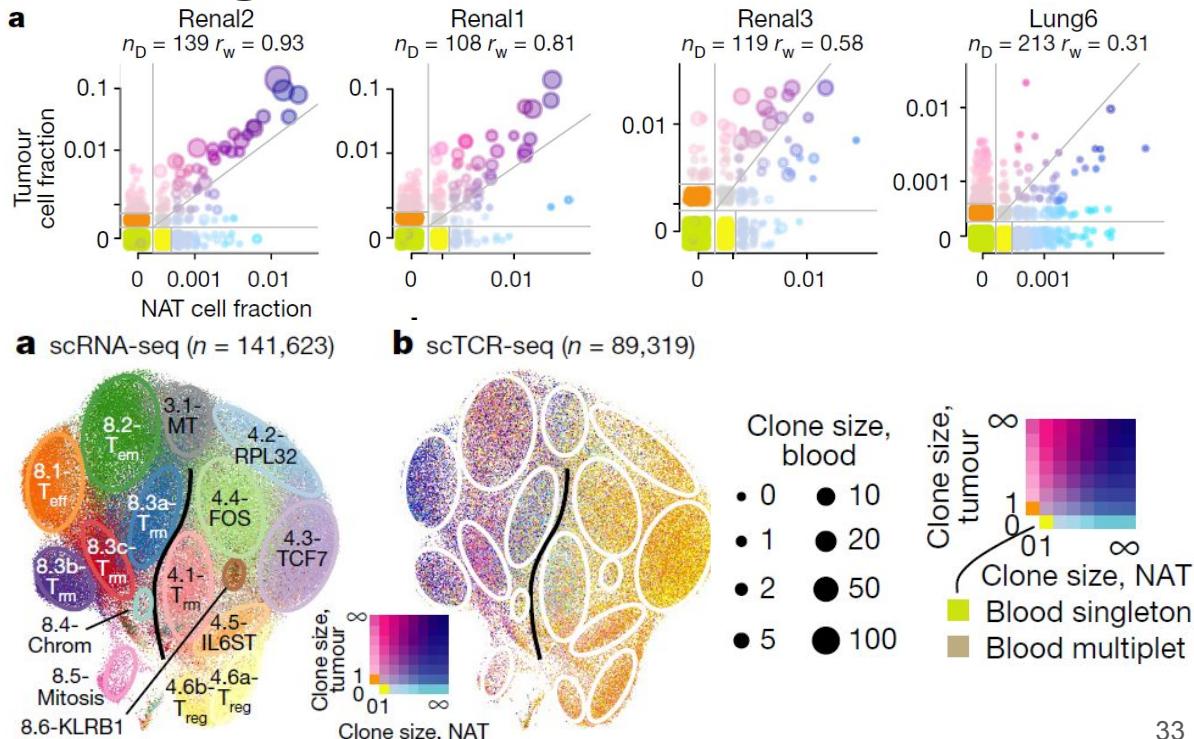
The multivariate classifier improves performance, but to predict responsiveness is an open question

Testing of TMB versus multivariable CPI stratifier performance in three independent test cohorts (total n=341):



Wu et al. characterized T cells in tumour, normal adjacent tissue (NAT), and blood using single-cell RNA and TCR sequencing

- Expanded clonotypes (T cells) found in the tumour and normal adjacent tissue can also typically be detected in peripheral blood.
- Intra-tumoural T cells, especially in responsive patients, are replenished with fresh, non-exhausted replacement cells from sites outside the tumour.



Caveats and challenge

- The curse of dimensionality
- Separation of mechanistic modelling and of statistical modelling
- Lack of causal models

Conclusions

- Biomarkers (1) guide compound optimization and differentiation in preclinical studies, (2) support human dose prediction in translational PK/PD studies, and (3) allow patient stratification in clinical trials;
- Mathematical and computational biology is indispensable for biomarker identification;
- Caveats in biomarker identification calls for integrated mechanistic and statistical modelling to establish causal relations.

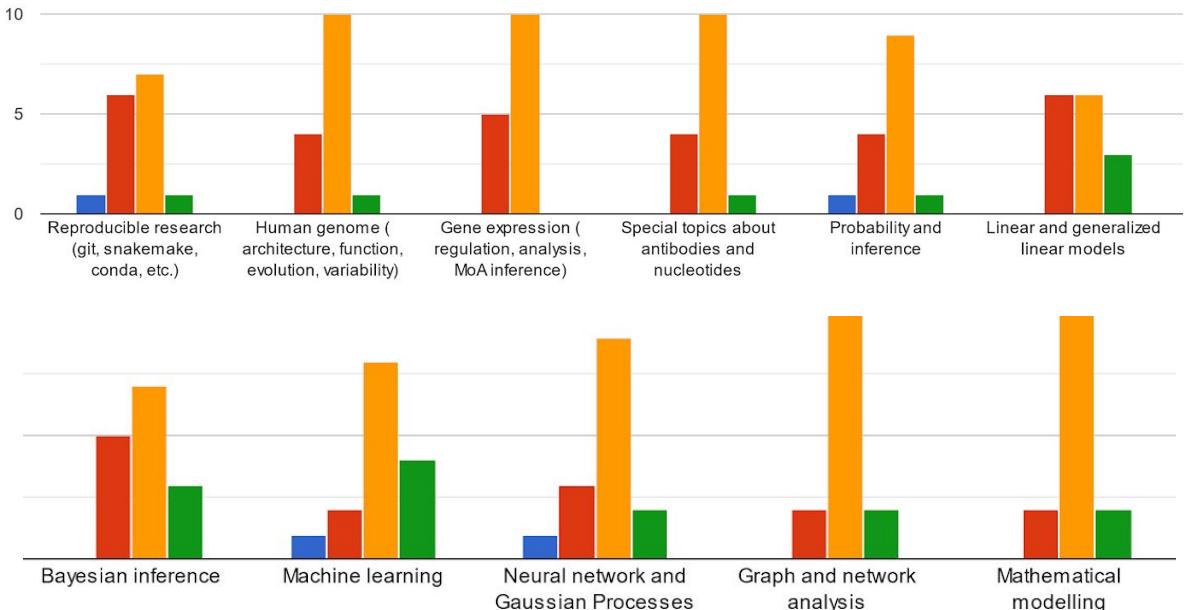
Evaluation of the MCBDD course 2021

Link: <https://k11331.evasys.de/evasys/online.php?pswd=5YS7K>

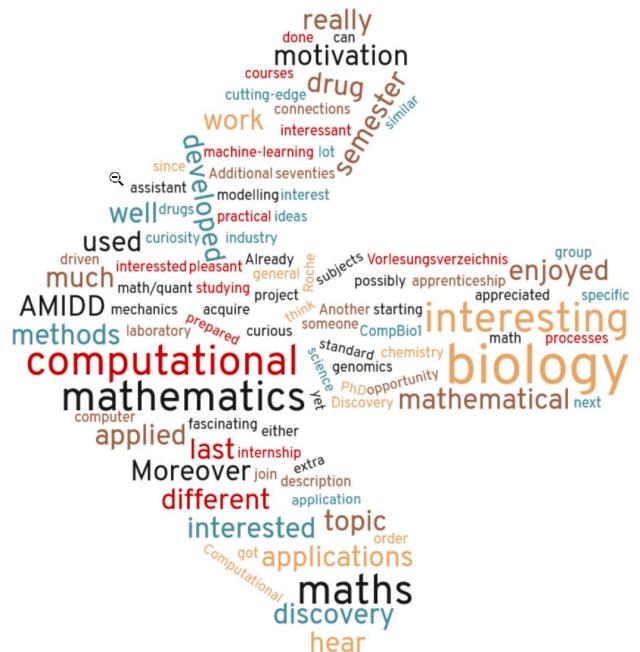
Bradford Hill Criteria for causation

1. **Strength** (effect size)
2. **Consistency** (reproducibility)
3. ***Specificity***
4. **Temporality**
5. **Biological gradient** (dose-response relationship)
6. ***Plausibility***
7. **Coherence**
8. **Experiment**
9. **Analogy** (similarity)
10. **Reversibility (proposed by others)**

Not at all interested Somehow interested Very interested I know the topic already very well



Your interest and motivation motivate me



A large, semi-transparent cloud of text in various colors (red, orange, yellow, green, blue) containing words such as:

- motivation, drug, semester, similar, done, can, work, interesting, machine-learning, lot, Additional severities, modelling interest, practical ideas, well, drugs, assistant, developed, since, driven, interested, pleasant, general, math/quant, studying, project, Vorlesungsverzeichnis, subjects, Vorlesungsverzeichnis, possibly apprenticeship, appreciated, specific, enjoyed, group, enjoyed, interesting, biology, computational, mathematics, methods, mechanics, acquire, curious, think, someone, starting, CompBiol, science, genomics, opportunity, mathematical, next, yet, Discovery, mathematical, next, computer, applied, last, internship, extra, Moreover, join, description, application, different, interested, topic, order, got, applications, Computational, maths, discovery, hear.

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